CLAIMS

1. Isolated sulfenyl amide cysteine-containing protein, or a homologue, allelic form, species variant, derivative or mutein thereof.

2. Isolated protein sulfenyl amide characterised by the HC(X5)R signature motif, or a homologue, allelic form, species variant, derivative or mutein thereof.

3. Isolated PTP sulfenyl amide, or a homologue, allelic form, species variant, derivative or mutein thereof.

4. A process for screening for an inhibitor of a protein (such as PTP) capable of forming a sulfenyl amide as defined in any one of claims 1 to 3, which process comprises the steps of: (a) providing a sulfenyl amide of the protein (e.g. PTP sulfenyl amide) (or a homologue, allelic form, species variant, derivative or mutein thereof); (b) contacting the sulfenyl amide of step (a) with a test compound; and (c) determining whether the test compound binds to the sulfenyl amide.

5. A process for producing an inhibitor of a protein (such as PTP) capable of forming a sulfenyl amide as defined in any one of claims 1 to 3, which process comprises the steps of: (a) providing a sulfenyl amide of the protein (e.g. PTP sulfenyl amide) (or a homologue, allelic form, species variant, derivative or mutein thereof); (b) contacting the sulfenyl amide of step (a) with a test compound; (c) determining whether the test compound binds to the sulfenyl amide; and (d) identifying the test compound as an inhibitor (e.g. a PTP inhibitor) on the basis of its ability to prevent or inhibit the reductive activation of the sulfenyl amide (e.g. PTP sulfenyl amide) to active protein (e.g. PTP).

6. The process of claim 5 wherein at least two chemically distinct test compounds are identified in step (d) and wherein the process further comprises the step of linking two or more of the chemically distinct compounds to produce a multimeric inhibitor.

7. The process of claim 5 or claim 6 for producing a pharmaceutical composition further comprising the step of: (e) incorporating the inhibitor identified in step (d) into a pharmaceutical excipient.

8. The sulfenyl amide of any one of claims 1 to 3 which is suitable for use in the process of any one of claims 4 to 7.

9. A protein (e.g. PTP) inhibitor obtainable by, or obtained by, the process of any one of claims 4 to 6.

10. A pharmaceutical composition obtainable by, or obtained by, the process of claim 7.

11. Use of a protein sulfenyl amide (e.g. PTP sulfenyl amide) for drug screening.

12. The use of a compound for the manufacture of a medicament for the treatment of a disease or condition mediated by protein tyrosine phosphatase, wherein the compound is one that binds to protein tyrosine phosphatase sulfenyl amide to prevent or inhibit conversion of the protein tyrosine phosphatase sulfenyl amide to an active reduced form of the protein tyrosine phosphatase.

13. A method of reducing the activity of a protein tyrosine phosphotase (PTP), the PTP being one which is convertible between an active form and an inactive form, the inactive form being characterised by the presence of a sulfenyl amide moiety formed at the active site of the PTP between the sulphur atom of a cysteine group and a backbone nitrogen atom of a neighbouring amino acid, whereby the sulfenyl amide moiety distorts and inactivates the active site of the PTP and wherein the sulfenyl amide moiety is disruptible to restore the inactivate form of the PTP to the active form thereof;
which method comprises inhibiting disruption of the sulfenyl amide moiety, or modifying the sulfenyl amide moiety to prevent restoration of the inactive form of the PTP to the active form.

14. A method according to claim 13 wherein the sulfenyl amide moiety is disruptible by reaction with a reducing agent to restore the inactivate form of the PTP to the active form thereof.

15. A method according to claim 13 or claim 14 wherein the sulfenyl amide moiety is disruptible to regenerate the cysteine group.

16. A method according to claim any one of claims 13 to 15 which comprises inhibiting disruption of the sulfenyl amide moiety by means of a ligand that binds to the inactivated active site of the PTP.

17. A method according to any one of claims 13 to 15 which comprises modifying the sulfenyl amide moiety to prevent restoration of the inactive form of the PTP to the active form.

18. A method according to claim 17 which comprises reversibly modifying the sulfenyl amide moiety.

19. A method according to claim 17 which comprises irreversibly modifying the sulfenyl amide moiety.

20. A method according to any one of claims 17 to 19 in which the sulfenyl amide moiety is modified by reaction with a nucleophilic ligand.

21. A method according to claim 20 wherein the sulfenyl amide moiety is modified by reaction with a nucleophilic ligand having a nucleophilic group that will react with the sulfenyl amide moiety, and a binding region for binding to the PTP sulfenyl amide in the region of the sulfenyl amide moiety.

22. A method according to claim 21 wherein the nucleophilic group is selected from the group consisting of a thiol, disulfane, primary thioamide, secondary thioamide, primary thiourea, secondary thiourea, primary amine, secondary amine, primary hydrazine, secondary hydrazine, primary hydrazide, secondary hydrazide, primary hydrazone, secondary hydrazone,

primary amide, secondary amide, primary urea, secondary urea, primary sulfonamide, secondary sulfonamide, 5-membered ring heterocycle containing NH, alcohol, hydroxylamine, oxime, hydroxamic acid, carboxylic acid (preferably other than an oxalamic acid), sulfoxide, sulfate and a nitrone.

23. A method of identifying by rational drug design a compound capable of reducing the level of activity of a protein tyrosine phosphate (PTP) in a cellular environment, the PTP being one which is convertible in a cellular environment between an active form and an inactive form, the inactive form being characterised by the presence of a sulfenyl amide moiety formed at the active site of the PTP between the sulphur atom of a cysteine group and a backbone nitrogen atom of a neighbouring amino acid;
which method comprises:
(a) designing a ligand that will (i) bind to the active site in the region of the sulfenyl amide moiety to inhibit conversion of the inactive form back to the active form, or (ii) modify the sulfenyl amide moiety to inhibit conversion of the inactive form of the PTP to the active form;
(b) synthesizing the ligand; and
(c) determining whether the ligand reduces the level of activity of a protein tyrosine phosphate (PTP) in a cellular environment.

24. A method according to claim 23 wherein the PTP is PTP1B and the ligand is one which is capable of binding to the sulfenyl amide PTP1B at a binding site as defined in any one of claims 52 to 65

25. A method according to any one of the preceding claims wherein the protein tyrosine phosphatase is characterised by a signature sequence of the formula: (I/V)HCXAGXXR(S/T/G) at a catalytic site thereof wherein the amino acid C is cysteine 215, and wherein the sulfenyl amide moiety is formed between the sulphur atom of cysteine 215 and a backbone nitrogen atom of a neighbouring amino acid.

26. A crystal of sulfenyl amide protein tyrosine phosphatase 1B.

27. A crystal of sulfenyl amide protein tyrosine phosphatase 1B having a Unit cell dimensions: a = 87.686 Å, b = 87.686 Å, c = 103.721 Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 120.00°$ and a space group: $P3_1\,2\,1$.

28. A crystal of sulfenyl amide protein tyrosine phosphatase 1B having a resolution better than, i.e. numerically lower than, 3.0 Å.

29. A crystal of sulfenyl amide protein tyrosine phosphatase 1B having the structure defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

30. A method of homology modeling comprising the steps of: (a) aligning a representation of an amino acid sequence of a target sulfenyl amide protein tyrosine phosphatase protein of unknown three-dimensional structure with the amino acid sequence of the sulfenyl amide protein tyrosine phosphatase 1B of Table 1 or Table 2 to match homologous regions of the amino acid sequences; (b) modeling the structure of the matched homologous regions of said target sulfenyl amide protein tyrosine phosphatase of unknown structure on the corresponding regions of the sulfenyl amide protein tyrosine phosphatase 1B structure as defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; and (c) determining a conformation (e.g. so that favorable interactions are formed within the target sulfenyl amide protein tyrosine phosphatase of unknown structure and/or so that a low energy conformation is formed) for said target sulfenyl amide protein tyrosine phosphatase of unknown structure which substantially preserves the structure of said matched homologous regions.

31. A method according to claim 30 wherein one or all of steps (a) to (c) are performed by computer modeling.

32. A method for determining the structure of a protein, which method comprises; providing the co-ordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å, and either (a)

positioning the co-ordinates in the crystal unit cell of said protein so as to provide a structure for said protein or (b) assigning NMR spectra peaks of said protein by manipulating the coordinates of Table 1 or Table 2.

33. A method according to claim 32 wherein the co-ordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å are used to solve the structure of a target sulfenyl amide protein tyrosine phosphatase, particularly homologues of sulfenyl amide protein tyrosine phosphatase 1B for example PTP-α, T-cell PTP, or LAR.

34. A system, particularly a computer system, the system containing either (a) atomic coordinate data according to Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å, said data defining the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B or at least selected coordinates thereof; (b) structure factor data (where a structure factor comprises the amplitude and phase of the diffracted wave) for sulfenyl amide protein tyrosine phosphatase 1B, said structure factor data being derivable from the atomic coordinate data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (c) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase protein generated by homology of the target based on the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (d) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; or (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

35. A computer-readable storage medium, comprising a data storage material encoded with computer readable data, wherein the data are defined by all or a portion (e.g. selected coordinates as defined herein) of the structure coordinates of sulfenyl amide protein tyrosine phosphatase 1B of Table 1 or

Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å, or a homologue of sulfenyl amide protein tyrosine phosphatase 1B, wherein said homologue comprises backbone atoms that have a root mean square deviation from the backbone atoms (nitrogen-carbon$_\alpha$-carbon) of Table 1 or Table 2 of not more than 1.5 Å.

36. A computer-readable data storage medium comprising a data storage material encoded with a first set of computer-readable data comprising a Fourier Transform of at least a portion (e.g. selected coordinates as defined herein) of the structural coordinates for sulfenyl amide protein tyrosine phosphatase 1B according to Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; which, when combined with a second set of machine readable data comprising an X-ray diffraction pattern of a molecule or molecular complex of unknown structure, using a machine programmed with the instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

37. Computer readable media with at least one of: (a) atomic coordinate data according to Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å recorded thereon, said data defining the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B, or at least selected coordinates thereof; (b) structure factor data for sulfenyl amide protein tyrosine phosphatase 1B recorded thereon, the structure factor data being derivable from the atomic coordinate data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (c) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase protein generated by homology modeling of the target based on the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (d) atomic coordinate data of a sulfenyl amide protein tyrosine phosphatase 1B-ligand complex or a sulfenyl amide protein tyrosine phosphatase 1B homologue or analogue generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1

or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

38. A method of providing data for generating structures and/or performing rational drug design for sulfenyl amide protein tyrosine phosphatase 1B, sulfenyl amide protein tyrosine phosphatase 1B homologues or analogues, complexes of sulfenyl amide protein tyrosine phosphatase 1B with a candidate modulator, or complexes of sulfenyl amide protein tyrosine phosphatase 1B homologues or analogues with candidate modulators, the method comprising:

(i) establishing communication with a remote device containing computer-readable data comprising at least one of: (a) atomic coordinate data according to Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å, said data defining the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B, at least one sub-domain of the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B, or the coordinates of a portion of atoms of sulfenyl amide protein tyrosine phosphatase 1B; (b) structure factor data for sulfenyl amide protein tyrosine phosphatase 1B, said structure factor data being derivable from the atomic coordinate data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (c) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase 1B homologue or analogue generated by homology modeling of the target based on the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (d) atomic coordinate data of a protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d); and

(ii) receiving said computer-readable data from said remote device.

39. A computer-based method of rational drug design which comprises:

providing the structure of the PTP1b sulfenyl amide as defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å;

providing the structure of a candidate modulator molecule; and

fitting the structure of candidate to the structure of the sulfenyl amide of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

40. A method of rational drug design which comprises;

providing the structure of the PTP1B sulfenyl amide as defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å;

providing the structure of a candidate compound; and

fitting the structure of the candidate compound to the structure of the sulfenyl amide as defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

41. A method of identifying by rational drug design a compound capable of reducing the level of activity of a protein tyrosine phosphatase (PTP) in a cellular environment, the PTP being one which is convertible in a cellular environment between an active form and an inactive or less active form, the inactive form or less active form being characterised by the presence of a sulfenyl amide moiety formed at the active site of the PTP between the sulphur atom of a cysteine group and a backbone nitrogen atom of a neighbouring amino acid;

which method comprises:

(a) designing a ligand that will (i) bind to the active site in the region of the sulfenyl amide moiety to inhibit conversion of the inactive form back to the active form, or (ii) modify the sulfenyl amide moiety to inhibit conversion of the inactive form of the PTP to the active form;

(b) synthesizing the ligand; and

(c) determining whether the ligand reduces the level of activity of a protein tyrosine phosphate (PTP) in a cellular environment.

42. A computer-based method of rational drug design which comprises:

providing the coordinates of at least two atoms of Table 1 or Table 2 of the PTP1B sulfenyl amide ("selected coordinates");

providing the structure of a candidate modulator molecule; and

fitting the structure of candidate to the selected coordinates of the PTP1B sulfenyl amide.

43. A method for determining the structure of a compound bound to sulfenyl amide PTP1B, said method comprising: (a) providing a crystal of sulfenyl amide PTP1b according to the invention; (b) soaking the crystal with said compounds; and (c) determining the structure of said sulfenyl amide PTP1b compound complex by employing the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

44. A method of inhibiting or preventing the reduction of sulfenyl amide PTB1B to PTB1B in a cellular environment by exposing the PTB1B to a ligand capable of binding to the sulfenyl amide PTB1B in the region of the sulfenyl amide moiety so as to prevent reduction of the sulfenyl amide moiety by an intracellular reducing agent.

45. A method of inhibiting or preventing the reduction of sulfenyl amide PTB1B to PTB1B in a cellular environment by exposing the PTB1B to a ligand capable of binding to the sulfenyl amide PTB1B in the region of the sulfenyl amide moiety, the ligand having a nucleophilic moiety capable of modifying the sulfenyl amide moiety so as to prevent its reduction by an intracellular reducing agent.

46. A method according to claim 44 or claim 45 wherein the ligand is capable of binding to the sulfenyl amide PTP1B at a binding site as defined in any one of claims 52 to 65.

47. A novel compound *per se* that inhibit protein tyrosine phosphatases by interacting with sulfenyl amide PTP to prevent or inhibit conversion of the PTP sulfenyl amide to an active form of the protein tyrosine phosphatase.

48. A compound according to claim 47 for use in medicine, for example for use in the treatment of diseases or conditions mediated by protein tyrosine phosphatase.

49. A compound according to claim 47 or claim 48 which is a non-covalent binding inhibitor that stabilises the sulfenyl-amide protein form.

50. A compound according to claim 47 or claim 48 which binds to and reversibly modifies the sulfenyl-amide form of the protein, e.g. by reacting with the sulfenyl amide moiety, and in so doing, preventing reactivation of the sulfenyl amide PTP by physiological cell cycling.

51. A compound according to claim 47 or claim 48 which binds to and irreversibly modifies the sulfenyl-amide form of the protein, e.g. by reacting irreversibly with the sulfenyl amide moiety, and in so doing, preventing reactivation of the sulfenyl amide PTP by physiological cell cycling.

52. A compound according to any one of claims 47 to 51, which compound is capable of binding to a first binding site of the sulfenyl amide PTP constituted by a groove lined by residues 41-47 of the phosphotyrosine recognition loop, residues 88-90, 115 to 120, residues 179 to 184 of the WPD-loop, residues 215 to 219 of the phosphate-binding cradle, and residues 262-266.

53. A compound according to claim 52 having a molecular shape and charge distribution that enables it to make polar interactions at the first binding site with one or more of:

(1) Lys41
(2) Asn42
(3) Arg45
(4) Tyr46
(5) Arg47
(6) Asn90
(7) Gln115

(8) Lys116
(9) Ser118
(10) Lys120
(11) Trp179
(12) Ser 216
(13) Arg221
(14) Gln262
(15) Thr263
(16) Asp265, and
(17) Gln266;

wherein the amino acid numbering refers to the numbering of the corresponding active form of PTP1B.

54. A compound according to claim 53 having a molecular shape and charge distribution that enables it to make polar interactions with two or more of moieties (1) to (17), more preferably three or more, for example four or more, and more particularly five or more.

55. A compound according to any one of claims 52 to 54 having a molecular shape and charge distribution that enables it to make hydrophobic interactions with one or more of:

(18) Leu88
(19) Pro89
(20) Leu119
(21) Phe182
(22) Gly183
(23) Val184
(24) Ala217
(25) Ile219
(26) the apolar part of Arg221, and
(27) the apolar part of Gln262.

56. A compound according to claim 55 having a molecular shape and charge distribution that enables it to make hydrophobic interactions with two or more of the moieties (18) to (27), more preferably three or more, for example five or more.

57. A compound according to any one of claims 47 to 56, which compound is capable of binding to a second binding site of the sulfenyl amide PTP constituted by a shallow depression defined by residues of the WPD-loop, the pTyr recognition loop and the loop containing residues 28-32.

58. A compound according to claim 57 having a molecular shape and charge distribution that enables it to make polar interactions at the second binding site with one or more of:

(44) Arg24
(14) Gln262
(45) Arg254
(46) Asn 44
(5) Arg47
(4) Tyr46
(1) Lys 41
(47) Lys36
(48) Asp29
(49) Cys32 and
(50) Ser50

59. A compound according to claim 57 or claim 58 having a molecular shape and charge distribution that enables it to make hydrophobic interactions with one or more of:

(51) Leu250
(14) Gln262
(41) Met258
(35) Val49
(4) Tyr46

(39) Gly218
(52) Gly259
(53) Phe52
(42) Leu260
(54) Leu261
(55) Ala35 and
(56) the backbone of Asp48.

60. A compound according to any one of claims 47 to 59, which compound is capable of binding to a third binding site in the form of a cavity having walls formed by Asp48, Val49, Leu83, Gly218, Gly220, Ser222, Arg257, Gly259, Gln262 and the sulfenyl-amide.

61. A compound according to claim 60 having a molecular shape and charge distribution that enables it to make polar interactions at the third binding site with one or more of:
(3) Arg45
(29) Asp48
(30) Ser222
(31) Arg257
(14) Gln262
(33) the protein backbone of one or more of (i) Thr84, (ii) Gly218, (iii) Gly220, (iv) Gly223, (v) Met258, (vi) and Gly259; and
(34) the sulfenyl-amide residue.

62. A compound according to claim 61 having a molecular shape and charge distribution that enables it to make polar interactions at two or more (more preferably three or more, four or more, or five or more) of the residues (3), (29) to (31), (14), (33) and (34).

63. A compound according to any one of claims 60 to 62 having a molecular shape and charge distribution that enables it to make hydrophobic interactions at the third binding site with one or more of:

(35) Val49
(36) Leu83
(37) Gln85
(38) Gly86
(39) Gly218
(40) Gly220
(41) Met258
(42) Leu260 and
(43) the main chain of His214.

64. A compound according to claim 50 or claim 51 which is a nucleophilic ligand, having a nucleophilic group that will react with the sulfenyl amide moiety, and a binding region for binding to the sulfenyl amide PTP in the region of the sulfenyl amide moiety.

65. A compound according to claim 64 wherein the binding region has a molecular shape and charge distribution that enables it to make an interaction with the first and second binding sites as defined in any one of claims 52 to 63.

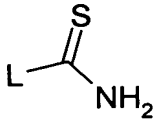
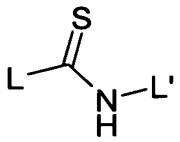
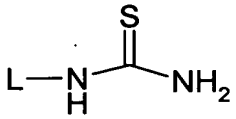
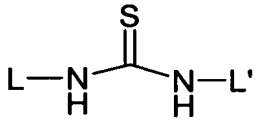
66. A compound according to claim 65 wherein the nucleophilic group contains a heteroatom (e.g. selected from nitrogen, sulphur, oxygen and phosphorus) that is either neutral or negatively charged, and which is capable of reacting with the sulfenyl amide species.

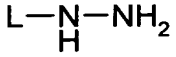
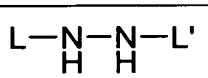
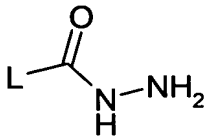
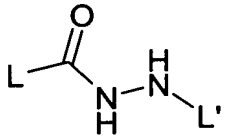
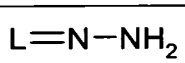
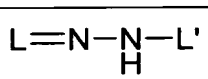
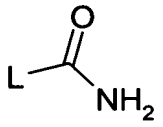
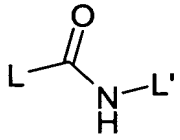
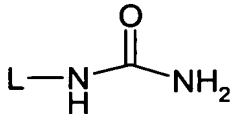
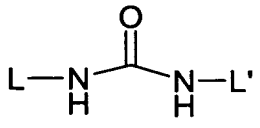
67. A compound according to claim 66 wherein the heteroatom is selected from nitrogen, oxygen and sulfur nucleophiles.

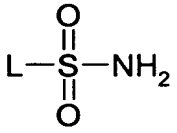
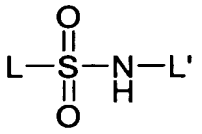
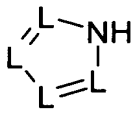
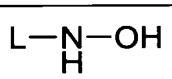
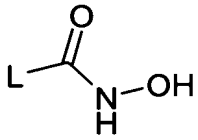
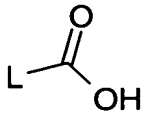
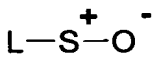
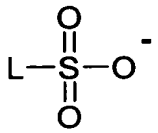
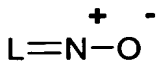
68. A compound according to claim 67 wherein the nucleophilic group is selected from the group consisting of a thiol, disulfane, primary thioamide, secondary thioamide, primary thiourea, secondary thiourea, primary amine, secondary amine, primary hydrazine, secondary hydrazine, primary hydrazide, secondary hydrazide, primary hydrazone, secondary hydrazone, primary amide, secondary amide, primary urea, secondary urea, primary

sulfonamide, secondary sulfonamide, 5-membered ring heterocycle containing NH, alcohol, hydroxylamine, oxime, hydroxamic acid, carboxylic acid (preferably other than an oxalamic acid), sulfoxide, sulfate and a nitrone.

69. A compound according to claim 67 or claim 68 wherein the nucleophile is selected from the group consisting of the nucleophiles set out in Table 3 below, and L is the residue of the compound.

Type of nucleophile	**Structure**	**Name**
Sulphur	L—SH	Thiol
	L—S—SH	Disulfane
		Primary Thioamide
		Secondary Thioamide
		Primary thiourea
		Secondary thiourea
Nitrogen	L—NH_2	Primary amine
		Secondary amine

		Primary Hydrazine
		Secondary Hydrazine
		Primary Hydrazide
		Secondary Hydrazide
		Primary Hydrazone
		Secondary Hydrazone
		Primary amide
		Secondary amide
		Primary urea
		Secondary urea

		Primary Sulfonamide
		Secondary Sulfonamide
		5-membered ring heterocycle containing NH
Oxygen	L—OH	Alcohol
		Hydroxylamine
	L=N—OH	Oxime
		Hydroxamic acid
		Carboxylic acid (preferably not oxalamic acids)
		Sulfoxide
		Sulfate
		Nitrone

70. A compound according to any one of claims 47 to 69 which comprises a scaffold formed from one or more optionally substituted carbocyclic or heterocyclic ring systems, the ring systems and/or the substituents having one or more polar or non-polar moieties for interacting with the first and/or second binding sites.

71. A compound according to claim 70 wherein the carbocyclic and heterocyclic ring systems contain at least one an aromatic ring having from 5 to 12 ring members, more usually from 5 to 10 ring members.

72. A compound according to claim 71 containing a heteroaryl group which is a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings, each ring for example containing up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen, preferably up to 3 heteroatoms, more usually up to 2, for example a single heteroatom.

73. A compound according to claim 72 wherein the heteroaryl group is selected from the group consisting of pyridyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, triazinyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, benzfuranyl, benzthiophenyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, isobenzofuranyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adenine, guanine), indazolyl, benzodioxolyl, chromenyl, isochromenyl, chroman, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

74. A compound according to claim 71 containing at least one carbocyclic aryl group selected from the group consisting of phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

75. A compound according to claim 70 containing at least one non-aromatic heterocyclic group having from 3 to 12 ring members, more usually 5 to 10 ring members.

76. A compound according to claim 75 wherein the non-aromatic heterocyclic group is monocyclic or bicyclic, and is optionally selected from the group consisting of cyclic ether moieties (e.g as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene), cyclic amine moieties (e.g. as in pyrrolidine), cyclic sulphones (e.g. as in sulfolane and sulfolene)), cyclic sulphoxides, cyclic sulphonamides and combinations thereof.

77. A compound according to claim 76 wherein the non-aromatic heterocyclic group is selected from the group consisting of morpholine, piperidine, pyrrolidine, pyrrolidone, tetrahydrofuran, tetrahydrothiophene, dioxan, tetrahydropyran, imidazoline, imidazolidinone, oxazoline, thiazoline, piperazine, and N-alkyl piperazines such as N-methyl piperazine.

78. A compound according to any one of claims 70 to 77 wherein the carbocyclic and heterocyclic groups are substituted by one or more substituent groups selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

79. A pharmaceutical composition comprising a compound as defined in any one of claims 47 to 78 and a pharmaceutically acceptable excipient.

80. A compound as defined in any one of claims 47 to 78 for use in medicine, for example in the prevention or treatment of a disease state or condition mediated by PTP such as PTP1B.

81. The use of a compound as defined in anyone of claims 47 to 78 for the manufacture of a medicament for the prevention or treatment of a disease state or condition mediated by PTP such as PTP1B.

82. A method for the prevention or treatment of a disease state or condition mediated by PTP such as PTP1B in a patient (e.g. a human patient) in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound as defined in any one of claim 47 to 78.

83. A use, method, or compound for use as defined in any one claims 80 to 82 wherein the disease state or condition mediated by PTP such as PTP1B is selected from cancer, diabetes, rheumatoid arthritis and hypertension.

84. A three-dimensional representation of a PTP sulfenyl amide or a portion of a PTP sulfenyl amide, which representation comprises all or a portion of the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

85. The three-dimensional representation of claim 84, which is a model constructed from all or a portion of the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

86. The model of claim 85 wherein the portion of PTP sulfenyl amide is a binding cavity and the portion of the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å

comprise those of atoms defining a binding site within the binding cavity (for example, the "selected coordinates" as defined herein).

87. A three-dimensional representation of a compound, which fits the model of claim 85 or claim 86 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

88. The three-dimensional representation of claim 87, which is a model of the compound.

89. The model of claim 88 wherein the compound is a pharmacophore.

90. The model of any one of claims 85, 86, 88 or 89 which is: (a) a wire-frame model; (b) a chicken-wire model; (c) a ball-and-stick model; (d) a space-filling model; (e) a stick-model; (f) a ribbon model; (g) a snake model; (h) an arrow and cylinder model; (i) an electron density map; (j) a molecular surface model.

91. The model of any one of claims 85, 86, 88, 89 or 90 which is in physical form.

92. The model of any one of claims 85, 86, 88, 89 or 90 which is in electronic form.

93. The model of claim 92, which comprises a graphical image display on a computer screen.

94. A computer-based method for the analysis of the interaction of a molecular structure with a PTP sulfenyl amide structure of the invention, which comprises: (a) providing a PTP sulfenyl amide model as defined in claim 85, 86 or 90 to 93; (b) providing a molecular structure to be fitted to said PTP sulfenyl amide model; and (c) fitting the molecular structure to the PTP sulfenyl amide model to produce a compound model as defined in claim 88, 89 or 90 to 93.